09/276,868

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=> file medline biosis caplus uspatfull

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CA INDEXING COPYRIGHT (C) 2000 AMERICAN CHEMICAL SOCIETY (ACS)

=> s arg arg arg pro arg pro pro tyr

L8            4 ARG ARG ARG PRO ARG PRO PRO TYR

=> s angiogenesis

L9        25992 ANGIOGENESIS

=> s l8 and l9

L10           2 L8 AND L9

=> d l10 1-2


L10  ANSWER 1 OF 2  USPATFULL
AN      1999:12906  USPATFULL
TI      Synducin mediated modulation of tissue repair
IN      Gallo, Richard L., Natick, MA, United States
        Bernfield, Merton, Boston, MA, United States
PA      Children's Medical Center Corporation, Boston, MA, United States (U.S.
        corporation)
PI      US 5863897  19990126
AI      US 1996-728333  19961010 (8)
RLI     Continuation of Ser. No. US 1994-310722, filed on 22 Sep 1994, now
        patented, Pat. No. US 5654273
DT      Utility
LN.CNT 666
INCL    INCLM: 514/012.000
        INCLS: 514/008.000
NCL     NCLM:  514/012.000
        NCLS:  514/008.000
IC      [6]
        ICM: A61K038-00
        ICS: A61K038-02; C07K005-00; C07K007-00
EXF     514/12; 514/8; 530/324
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
```

L10 ANSWER 2 OF 2 USPATFULL
AN 97:68443 U[redacted]FULL
TI Synducin mediated modulation of tissue repair
IN Gallo, Richard L., Natick, MA, United States
Bernfield, Merton, Boston, MA, United States
PA Children's Medical Center Corporation, Boston, MA, United States (U.S. corporation)
PI US 5654273 19970805
AI US 1994-310722 19940922 (8)
DT Utility
LN.CNT 748
INCL INCLM: 514/012.000
INCLS: 514/008.000; 530/324.000
NCL NCLM: 514/012.000
NCLS: 514/008.000; 530/324.000
IC [6]
ICM: A61K038-00
ICS: C07K005-00; C07K007-00; C07K017-00
EXF 514/12; 514/8; 530/324
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

=> d l10 1-2 ab kwic

L10 ANSWER 1 OF 2 USPATFULL

AB The membrane permeating antibacterial peptide, PR-39, previously found only in the intestine, was purified from wound fluid and shown to possess syndecan-1 and syndecan-4 inductive activity specifically in mesenchymal cells. This is a newly recognized function that defines peptide containing syndecan-inducing activity, and that are known as synducins. Therefore a molecule with both antimicrobial and synducin activities is deposited in wounds where it can simultaneously reduce infection and influence the action of growth factors, matrix components, and other cellular effectors involved in wound repair. Synducins, including PR-39, and derivatives thereof, is therefore useful in the modulation of wound healing, as well as other disorders involving mesenchymal cells and cell surface molecular interaction, including metastatic disease, **angiogenesis**, restenosis, stasis or decubitis ulcers, and prevention of keloids.

AB . . . modulation of wound healing, as well as other disorders involving mesenchymal cells and cell surface molecular interaction, including metastatic disease, **angiogenesis**, restenosis, stasis or decubitis ulcers, and prevention of keloids.

SUMM . . . healing, as well as other disorders involving mesenchymal cells and ligand interactions with cell surface heparan sulfate, including metastatic disease, **angiogenesis**, restenosis, stasis or decubitis ulcers, and prevention of keloids.

DETD PR-39 is the 39 amino acid sequence shown in Sequence ID No. 1,

Arg Arg Arg Pro Arg
Pro Pro Tyr Leu Pro Arg Pro Arg Pro Pro Pro
Phe Phe Pro Pro Arg Leu Pro Pro Arg Ile Pro Pro. . .

DETD . . . molecules that interact with the syndecans have known in vivo effects: basic fibroblast growth factor (bFGF) accelerates wound repair and **angiogenesis**, as reported by McGee, et al., J. Surg. Res. 45, 145-153 (1988) and Salmivirta, et al., J. Biol. Chem. 267(25), 17606-17610 (1992); platelet derived growth factor (PDGF) induces vascular restenosis and **angiogenesis**; and vascular endothelial growth factor (VEGF) induces **angiogenesis**. Extracellular matrix components have similarly known effects: both fibronectin fragments and laminin fragments are anti-metastatic and are known to bind. . .

DETD . . . 39 amino acids. Sequencing established the N-terminal 36 amino acids unequivocally without detection of minor sequences, Seq. ID No. 1,

Arg Arg Arg Pro Arg
Pro Pro Tyr Leu Pro Arg Pro Arg Pro Pro Pro
Phe Phe Pro Pro Arg Leu Pro Pro Arg Ile Pro Pro. . .

CLM What is claimed is:
9. The method of claim 3 wherein the synducin is administered in an amount effective to induce **angiogenesis** at a site in need thereof.

L10 ANSWER 2 OF 2 USPATFULL

AB The membrane permeating antibacterial peptide, PR-39, previously found only in the intestine, was purified from wound fluid and shown to possess syndecan-1 and syndecan-4 inductive activity specifically in

mesenchymal cells. This is a newly recognized function that defines peptide containing syndecan-inducing activity and that are known as synducins. Therefore a molecule with both antimicrobial and synducin activities is deposited in wounds where it can simultaneously reduce infection and influence the action of growth factors, matrix components,
and other cellular effectors involved in wound repair. Synducins, including PR-39, and derivatives thereof, is therefore useful in the modulation of wound healing, as well as other disorders involving mesenchymal cells and cell surface molecular interaction, including metastatic disease, **angiogenesis**, restenosis, stasis or decubitis ulcers, and prevention of keloids.

AB . . . modulation of wound healing, as well as other disorders involving mesenchymal cells and cell surface molecular interaction, including metastatic disease, **angiogenesis**, restenosis, stasis or decubitis ulcers, and prevention of keloids.

SUMM . . . healing, as well as other disorders involving mesenchymal cells
and ligand interactions with cell surface heparan sulfate, including metastatic disease, **angiogenesis**, restenosis, stasis or decubitis ulcers, and prevention of keloids.

DRWD PR-39 is the 39 amino acid sequence shown in Sequence ID No. 1,

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Pro Pro Tyr Leu Pro Arg Pro Arg Pro Pro Pro
Phe Phe Pro Pro Arg Leu Pro Pro Arg Ile Pro Pro. . .

DRWD . . . molecules that interact with the syndecans have known in vivo effects: basic fibroblast growth factor (bFGF) accelerates wound repair and **angiogenesis**, as reported by McGee, et al., J. Surg. Res. 45, 145-153 (1988) and Salmivirta, et al., J. Biol. Chem. 267(25), 17606-17610 (1992); platelet derived growth factor (PDGF) induces vascular restenosis and **angiogenesis**; and vascular endothelial growth factor (VEGF) induces **angiogenesis**. Extracellular matrix components have similarly known effects: both fibronectin fragments and laminin fragments are anti-metastatic and are known to bind. . .

DETD . . . 39 amino acids. Sequencing established the N-terminal 36 amino acids unequivocally without detection of minor sequences, Seq. ID No. 1,

Arg Arg Arg Pro Arg
Pro Pro Tyr Leu Pro Arg Pro Arg Pro Pro Pro
Phe Phe Pro Pro Arg Leu Pro Pro Arg Ile Pro Pro. . .

=> d l8 1-4

L8 ANSWER 1 OF 4 CAPLUS COPYRIGHT 2000 ACS
AN 1993:400919 CAPLUS
DN 119:919
TI Polypeptides and their use as antibacterial agents
IN Lee, Jong Youn; Boman, Hans G.; Mutt, Viktor; Joernvall, Hans
PA Swed.
SO PCT Int. Appl., 15 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9222578	A1	19921223	WO 1992-SE394	19920610
	W: AU, CA, HU, JP, US				
	RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LU, MC, NL, SE				
	SE 9101838	A	19921215	SE 1991-1838	19910614
	SE 468516	B	19930201		
	CA 2111340	AA	19921223	CA 1992-2111340	19920610
	AU 9220220	A1	19930112	AU 1992-20220	19920610
	AU 667472	B2	19960328		
	EP 589995	A1	19940406	EP 1992-912631	19920610
	EP 589995	B1	19990324		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, MC, NL				
	AT 178072	E	19990415	AT 1992-912631	19920610
	ES 2131528	T3	19990801	ES 1992-912631	19920610
	US 5489575	A	19960206	US 1994-162052	19940602
PRAI	SE 1991-1838	19910614			
	WO 1992-SE394	19920610			

L8 ANSWER 2 OF 4 USPATFULL
AN 1999:12906 USPATFULL
TI Synducin mediated modulation of tissue repair
IN Gallo, Richard L., Natick, MA, United States
Bernfield, Merton, Boston, MA, United States
PA Children's Medical Center Corporation, Boston, MA, United States (U.S. corporation)
PI US 5863897 19990126
AI US 1996-728333 19961010 (8)
RLI Continuation of Ser. No. US 1994-310722, filed on 22 Sep 1994, now patented, Pat. No. US 5654273
DT Utility
LN.CNT 666
INCL INCLM: 514/012.000
INCLS: 514/008.000
NCL NCLM: 514/012.000
NCLS: 514/008.000
IC [6]
ICM: A61K038-00
ICS: A61K038-02; C07K005-00; C07K007-00
EXF 514/12; 514/8; 530/324
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L8 ANSWER 3 OF 4 USPATFULL
AN 97:68443 USPATFULL

TI Synducin me[illegible]ted modulation of tissue repai[illegible]
IN Gallo, Rich[illegible] L., Natick, MA, United State[illegible]
Bernfield, Merton, Boston, MA, United States
PA Children's Medical Center Corporation, Boston, MA, United States (U.S. corporation)
PI US 5654273 19970805
AI US 1994-310722 19940922 (8)
DT Utility
LN.CNT 748
INCL INCLM: 514/012.000
INCLS: 514/008.000; 530/324.000
NCL NCLM: 514/012.000
NCLS: 514/008.000; 530/324.000
IC [6]
ICM: A61K038-00
ICS: C07K005-00; C07K007-00; C07K017-00
EXF 514/12; 514/8; 530/324
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L8 ANSWER 4 OF 4 USPATFULL
AN 96:11120 USPATFULL
TI Polypeptides and their use
IN Lee, Jong-Youn, Odengatan 23, Enskede, Sweden
Boman, Hans G., Odengatan 23, S-11424 Stockholm, Sweden
Mutt, Viktor, Solna, Sweden
Jornvall, Hans, Sundbyberg, Sweden
PA Boman, Hans G., Stockholm, Sweden (non-U.S. individual)
PI US 5489575 19960206
WO 9222578 19921223
AI US 1994-162052 19940602 (8)
WO 1992-SE394 19920610
19940602 PCT 371 date
19940602 PCT 102(e) date
PRAI SE 1991-1838 19910614
DT Utility
LN.CNT 313
INCL INCLM: 514/012.000
INCLS: 530/324.000
NCL NCLM: 514/012.000
NCLS: 530/324.000
IC [6]
ICM: A61K038-00
ICS: C07K005-00; C07K007-00; C07K017-00
EXF 530/324; 514/12

=> d l8 1-4 ab kwic

L8 ANSWER 1 OF 4 CAPLUS COPYRIGHT 2000 ACS
AB A polypeptide comprising the amino acid sequence of **Arg-Arg-Pro-Arg-Pro-Pro-Tyr**-Leu-Pro-Arg-Pro-Arg-Pro-Pro-Pro-Phe-Phe-Pro-Pro-Arg-Leu-Pro-Pro-Ile-Pro-Pro-Gly-Phe-Pro-Pro-Arg-Phe-Pro-Arg-Phe-Pro or its deriv. is orally or parenterally administered to patients to inhibit bacterial growth. A peptide conc. is prepd. from pig small intestine and purified. A fraction showing a highest activity against Escherichia coli was further tested against other bacteria.

AB A polypeptide comprising the amino acid sequence of **Arg-Arg-Pro-Arg-Pro-Pro-Tyr**-Leu-Pro-Arg-Pro-Arg-Pro-Pro-Pro-Phe-Phe-Pro-Pro-Arg-Leu-Pro-Pro-Ile-Pro-Pro-Gly-Phe-Pro-Pro-Arg-Phe-Pro-Arg-Phe-Pro or its deriv. is orally or parenterally administered to patients to inhibit bacterial growth. A peptide conc. is prepd. from. . .

L8 ANSWER 2 OF 4 USPATFULL
AB The membrane permeating antibacterial peptide, PR-39, previously found only in the intestine, was purified from wound fluid and shown to possess syndecan-1 and syndecan-4 inductive activity specifically in mesenchymal cells. This is a newly recognized function that defines peptide containing syndecan-inducing activity, and that are known as synducins. Therefore a molecule with both antimicrobial and synducin activities is deposited in wounds where it can simultaneously reduce infection and influence the action of growth factors, matrix components, and other cellular effectors involved in wound repair. Synducins, including PR-39, and derivatives thereof, is therefore useful in the modulation of wound healing, as well as other disorders involving mesenchymal cells and cell surface molecular interaction, including metastatic disease, angiogenesis, restenosis, stasis or decubitis ulcers, and prevention of keloids.

DETD PR-39 is the 39 amino acid sequence shown in Sequence ID No. 1, **Arg Arg Arg Pro Arg Pro Pro Tyr** Leu Pro Arg Pro Arg Pro Pro Pro Phe Phe Pro Pro Arg Leu Pro Pro Arg Ile Pro Pro. . .

DETD . . . 39 amino acids. Sequencing established the N-terminal 36 amino acids unequivocally without detection of minor sequences, Seq. ID No. 1, **Arg Arg Arg Pro Arg Pro Pro Tyr** Leu Pro Arg Pro Arg Pro Pro Pro Phe Phe Pro Pro Arg Leu Pro Pro Arg Ile Pro Pro. . .

L8 ANSWER 3 OF 4 USPATFULL
AB The membrane permeating antibacterial peptide, PR-39, previously found only in the intestine, was purified from wound fluid and shown to possess syndecan-1 and syndecan-4 inductive activity specifically in mesenchymal cells. This is a newly recognized function that defines peptide containing syndecan-inducing activity, and that are known as synducins. Therefore a molecule with both antimicrobial and synducin activities is deposited in wounds where it can simultaneously reduce infection and influence the action of growth factors, matrix components,

and other c[redacted]ular effectors involved in wo[redacted]repair. Synducins, including [redacted]9, and derivatives thereof, i[redacted]herefore useful in the modulation of wound healing, as well as other disorders involving mesenchymal cells and cell surface molecular interaction, including metastatic disease, angiogenesis, restenosis, stasis or decubitis ulcers, and prevention of keloids.

DRWD PR-39 is the 39 amino acid sequence shown in Sequence ID No. 1,

Arg Arg Arg Pro Arg
Pro Pro Tyr Leu Pro Arg Pro Arg Pro Pro Pro
Phe Phe Pro Pro Arg Leu Pro Pro Arg Ile Pro Pro. . .

DETD . . . 39 amino acids. Sequencing established the N-terminal 36 amino acids unequivocally without detection of minor sequences, Seq. ID No. 1,

Arg Arg Arg Pro Arg
Pro Pro Tyr Leu Pro Arg Pro Arg Pro Pro Pro
Phe Phe Pro Pro Arg Leu Pro Pro Arg Ile Pro Pro. . .

L8 ANSWER 4 OF 4 USPATFULL

AB Polypeptides comprising the following amino acid sequence: **Arg-Arg-Arg-Pro-Arg-Pro-Pro-Tyr**-Leu-Pro-Arg-Pro-Arg-Pro-Pro-Pro-Phe-Phe-Pro-Pro-Arg-Leu-Pro-Pro-Arg-Ile-Pro-Pro-Gly-Phe-Pro-Pro-Arg-Phe-Pro-Pro-Arg-Phe-Pro; pharmaceutical compositions containing such polypeptides; and a method of inhibiting bacterial growth using such polypeptides.

AB Polypeptides comprising the following amino acid sequence: **Arg-Arg-Arg-Pro-Arg-Pro-Pro-Tyr**-Leu-Pro-Arg-Pro-Arg-Pro-Pro-Pro-Phe-Phe-Pro-Pro-Arg-Leu-Pro-Pro-Arg-Ile-Pro-Pro-Gly-Phe-Pro-Pro-Arg-Phe-Pro-Pro-Arg-Phe-Pro; pharmaceutical compositions containing such polypeptides; and a method of inhibiting bacterial growth using such polypeptides.

SUMM **Arg-Arg-Arg-Pro-Arg-Pro-Pro-Tyr**-Leu-Pro-Arg-Pro-Arg-Pro-Pro-Pro-Phe-Phe-Pro-Pro-Arg-Leu-Pro-Pro-Arg-Ile-Pro-Pro-Gly-Phe-Pro-Pro-Arg-Phe-Pro-Pro-Arg-Phe-Pro,

CLM What is claimed is:

1. A bacteriocidal polypeptide which comprises a polypeptide consisting of the following amino acid sequence: **Arg-Arg-Arg-Pro-Arg-Pro-Pro-Tyr**-Leu-Pro-Arg-Pro-Arg-Pro-Pro-Pro-Phe-Phe-Pro-Pro-Arg-Leu-Pro-Pro-Arg-Ile-Pro-Pro-Gly-Phe-Pro-Pro-Arg-Phe-Pro-Pro-Arg-Phe-Pro.

=> d l18 1-2

L18 ANSWER 1 OF 2 USPATFULL
AN 1999:12906 USPATFULL
TI Synducin mediated modulation of tissue repair
IN Gallo, Richard L., Natick, MA, United States
Bernfield, Merton, Boston, MA, United States
PA Children's Medical Center Corporation, Boston, MA, United States (U.S. corporation)
PI US 5863897 19990126
AI US 1996-728333 19961010 (8)
RLI Continuation of Ser. No. US 1994-310722, filed on 22 Sep 1994, now patented, Pat. No. US 5654273
DT Utility
LN.CNT 666
INCL INCLM: 514/012.000
INCLS: 514/008.000
NCL NCLM: 514/012.000
NCLS: 514/008.000
IC [6]
ICM: A61K038-00
ICS: A61K038-02; C07K005-00; C07K007-00
EXF 514/12; 514/8; 530/324
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L18 ANSWER 2 OF 2 USPATFULL
AN 97:68443 USPATFULL
TI Synducin mediated modulation of tissue repair
IN Gallo, Richard L., Natick, MA, United States
Bernfield, Merton, Boston, MA, United States
PA Children's Medical Center Corporation, Boston, MA, United States (U.S. corporation)
PI US 5654273 19970805
AI US 1994-310722 19940922 (8)
DT Utility
LN.CNT 748
INCL INCLM: 514/012.000
INCLS: 514/008.000; 530/324.000
NCL NCLM: 514/012.000
NCLS: 514/008.000; 530/324.000
IC [6]
ICM: A61K038-00
ICS: C07K005-00; C07K007-00; C07K017-00
EXF 514/12; 514/8; 530/324
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L18 ANSWER 1 OF 2 USPATFULL

AB The membrane permeating antibacterial peptide, **PR-39**, previously found only in the intestine, was purified from wound fluid and shown to possess syndecan-1 and syndecan-4 inductive activity. .

infection and influence the action of growth factors, matrix components, and other cellular effectors involved in wound repair. Synducins, including **PR-39**, and derivatives thereof, is therefore useful in the modulation of wound healing, as well as other disorders involving mesenchymal cells and cell surface molecular interaction, including metastatic disease, **angiogenesis**, restenosis, stasis or decubitis ulcers, and prevention of keloids.

SUMM . . . to the effects of these extracellular matrix components that are involved in wound repair. Thus, the induction of syndecan-1 by **PR-39** may mediate growth factor responsiveness and the changes in cell proliferation, migration, and adhesion that must take place for wound. . .

SUMM . . . by increased syndecan-1 and -4 mRNA levels, stability at the cell surface and reduced glycosylation. The membrane permeating antibacterial peptide, **PR-39**, previously found only in the intestine, was purified from wound fluid and shown to possess this inductive activity. This newly. . .

SUMM Synducins, including **PR-39**, and derivatives thereof, are therefore useful in the modulation of wound healing, as well as other disorders involving mesenchymal cells and ligand interactions with cell surface heparan sulfate, including metastatic disease, **angiogenesis**, restenosis, stasis or decubitis ulcers, and prevention of keloids.

DRWD FIG. 3A is a graph of syndecan-1 (mOD/min) versus concentration of **PR-39** (.mu.M) showing that synthetic **PR-39** induces syndecan-1 in a dose dependent manner. Data represent the mean of triplicate determinations .+-.SD of a single experiment representative. . .

DRWD FIG. 3B is a graph of syndecan mRNA levels after culture of NIH-3T3 cells with synthetic **PR-39** (1 .mu.M) for 24 hours.

DRWD FIG. 4 is a graph showing uptake of **PR-39** by NIH-3T3 cells. The percent of radioactive **PR-39** (in cpm) specifically associated with the cells is plotted versus time of incubation until radioactive **PR-39** (in minutes), showing that **PR-39** is rapidly taken up by cells and reaches a saturation point.

DETD It has been discovered that a **39** amino acid peptide, **PR-39**, and biologically active derivatives thereof, induces syndecan-1 and -4 expression in mesenchymal cells. Methods for formulating pharmaceutical compositions and uses. . .

DETD **PR-39** is the **39** amino acid sequence shown in Sequence ID No. 1, **Arg Arg Arg Pro Arg Pro Pro Tyr** Leu Pro Arg Pro Arg Pro Pro Pro Phe Phe Pro Pro Arg Leu Pro Pro Arg Ile Pro Pro. . .

DETD **PR-39** can also be obtained from Magainin, Inc. of Plymouth Meeting, Pa.

DETD . . . molecules that interact with the syndecans have known in vivo effects: basic fibroblast growth factor (bFGF) accelerates wound repair

and **angiogenesis**, as reported by McGee, et al., J. Surg. Res. 45, 145-15[illegible]988) and Salmivirta, et al., [illegible]iol. Chem. 267(25), 17606-17610 (1992); platelet derived growth factor (PDGF) induces vascular restenosis and **angiogenesis**; and vascular endothelial growth factor (VEGF) induces **angiogenesis**. Extracellular matrix components have similarly known effects: both fibronectin fragments and laminin fragments are anti-metastatic and are known to bind. . .

DETD . . . 39 amino acids. Sequencing established the N-terminal 36 amino acids unequivocally without detection of minor sequences, Seq. ID No. 1,

Arg Arg Arg Pro Arg
Pro Pro Tyr Leu Pro Arg Pro Arg Pro Pro Pro
Phe Phe Pro Pro Arg Leu Pro Pro Arg Ile Pro Pro. . . Pro Arg Phe Pro Pro Arg Phe Pro. The sequence is identical with the N -terminal 36 amino acids of **PR-39**, a proline- and arginine-rich 39 amino acid peptide previously found in pig intestine, as described in PCT WO92/22578 by Lee,. . .

DETD Demonstration of syndecan-1 inducing activity of chemically synthesized **PR-39**.

DETD It was demonstrated that **PR-39** possesses syndecan inductive activity by treating NIH-3T3 cells with media containing synthetically prepared **PR-39**, as shown by FIGS. 3A and 3B. **PR-39** was synthesized by Chiron mimotopes peptide systems (San Diego, Calif.) and purity analysis performed by RP-HPLC and mass spectrometry. The. . . in 25% acetonitrile, 0.1% TFA, aliquoted for the indicated concentrations, lyophilized and reconstituted in culture media. Cells were exposed to **PR-39** in culture medium for 43 hours prior to determination of cell surface syndecan-1 levels by ELISA. Open boxes represent synthetically prepared **PR-39**, closed triangles represent structurally derived and purified **PR-39**. Data represent the mean of triplicate determinations .+-.SD of a single experiment representative of two experiments.

DETD Cell surface syndecan-1 was induced by synthetic **PR-39** in a concentration dependent manner, thereby demonstrating that syndecan-1 induction is due to **PR-39** and not to undetected trace contaminants present in the preparation from wound fluid.

DETD The results presented here demonstrate that an antibacterial peptide, **PR-39**, is in the fluid recovered from skin wounds and that it enhances the expression of cell surface syndecan-1 on mesenchymal. . .

DETD The uptake and binding characteristics of **PR-39**, Effect on Cell Permeability and Morphology.

DETD The uptake and binding of **PR-39** was demonstrated as follows. **PR-39** was iodinated using the Iodogen procedure (Pierce T). The influx and efflux kinetics were calculated, accessable compartments were evaluated, and. . .

DETD Cell permeability after **PR-39** treatment was then measured. NIH-3T3 cells were cultured to confluence on chamber slides. 0, 0.1, 0.5, 1, and 10 .mu.M **PR-39** was added to the culture medium and incubated 60 minutes at 37.degree. C.; then 50 .mu.g/ml propium iodide (FW 688) was added. A 2/20X field of fluorescent cells shown with **PR-39**, 100% (approximately 50/20X) with 0.1% Triton.TM. showed no large perability changes in the membrane.

DETD . . . determine the effect on cell morphology, NIH-3T3 cells were cultured to confluence on coverslips in 24 well plates. 2 .mu.M **PR-39** was added the medium and cultured for 72 hr. 2% PFA and acetone were used to fix cells and cells. . .

CLM What is claimed is:
4. The method of claim 1 wherein the synducin is **PR-39**

9. The method of claim 3 wherein the synducin is administered in an amount effective to induce **angiogenesis** at a site in need thereof.

15. The method of claim 3 wherein the synducin is **PR-39**.

=> d l18 2 kwic

L18 ANSWER 2 OF 2 USPATFULL

AB The membrane permeating antibacterial peptide, **PR-39**, previously found only in the intestine, was purified from wound fluid and shown to possess syndecan-1 and syndecan-4 inductive activity. .

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SUMM . . . to the effects of these extracellular matrix components that are involved in wound repair. Thus, the induction of syndecan-1 by **PR-39** may mediate growth factor responsiveness and the changes in cell proliferation, migration, and adhesion that must take place for wound. . .

SUMM . . . by increased syndecan-1 and -4 mRNA levels, stability at the cell surface and reduced glycosylation. The membrane permeating antibacterial peptide, **PR-39**, previously found only in the intestine, was purified from wound fluid and shown to possess this inductive activity. This newly. . .

SUMM Synducins, including **PR-39**, and derivatives thereof, are therefore useful in the modulation of wound healing, as well as other disorders involving mesenchymal cells and ligand interactions with cell surface heparan sulfate, including metastatic disease, **angiogenesis**, restenosis, stasis or decubitis ulcers, and prevention of keloids.

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DRWD FIG. 3B is a graph of syndecan mRNA levels after culture of NIH-3T3 cells with synthetic **PR-39** (1 .mu.M) for 24 hours.

DRWD FIG. 4 is a graph showing uptake of **PR-39** by NIH-3T3 cells. The percent of radioactive **PR-39** (in cpm) specifically associated with the cells is plotted versus time of incubation until radioactive **PR-39** (in minutes), showing that **PR-39** is rapidly taken up by cells and reaches a saturation point.

DRWD It has been discovered that a **39** amino acid peptide, **PR-39**, and biologically active derivatives thereof, induces syndecan-1 and -4 expression in mesenchymal cells. Methods for formulating pharmaceutical compositions and uses. . .

DRWD **PR-39** is the **39** amino acid sequence shown in Sequence ID No. 1, **Arg Arg Arg Pro Arg Pro Pro Tyr** Leu Pro Arg Pro Arg Pro Pro Pro Phe Phe Pro Pro Arg Leu Pro Pro Arg Ile Pro

Pro. . .

DRWD **PR-39** can [redacted] be obtained from Magainin, I[redacted] of Plymouth Meeting, Pa.

DRWD . . . molecules that interact with the syndecans have known in vivo effects: basic fibroblast growth factor (bFGF) accelerates wound repair and **angiogenesis**, as reported by McGee, et al., J. Surg. Res. 45, 145-153 (1988) and Salmivirta, et al., J. Biol. Chem. 267(25), 17606-17610 (1992); platelet derived growth factor (PDGF) induces vascular restenosis and **angiogenesis**; and vascular endothelial growth factor (VEGF) induces **angiogenesis**. Extracellular matrix components have similarly known effects: both fibronectin fragments and laminin fragments are anti-metastatic and are known to bind. . .

DETD . . . 39 amino acids. Sequencing established the N-terminal 36 amino acids unequivocally without detection of minor sequences, Seq. ID No. 1,

Arg Arg Arg Pro Arg
Pro Pro Tyr Leu Pro Arg Pro Arg Pro Pro Pro
Phe Phe Pro Pro Arg Leu Pro Pro Arg Ile Pro Pro. . . Pro Pro Arg Phe Pro Pro Arg Phe Pro. The sequence is identical with the N-terminal 36 amino acids of **PR-39**, a proline- and arginine-rich 39 amino acid peptide previously found in pig intestine, as described in

PCT WO92/22578 by Lee,. . .

DETD Demonstration of syndecan-1 inducing activity of chemically synthesized **PR-39**

DETD It was demonstrated that **PR-39** possesses syndecan inductive activity by treating NIH-3T3 cells with media containing synthetically prepared **PR-39**, as shown by FIGS. 3A and 3B. **PR-39** was synthesized by Chiron mimotopes peptide systems (San Diego, Calif.) and purity analysis performed by RP-HPLC and mass spectrometry. The. . . in 25% acetonitrile, 0.1% TFA, aliquoted for the indicated concentrations, lyophilized and reconstituted in culture media. Cells were exposed to **PR-39** in culture medium for 43 hours prior to determination of cell surface syndecan-1 levels by ELISA. Open boxes represent synthetically prepared **PR-39**, closed triangles represent structurally derived and purified **PR-39**. Data represent the mean of triplicate determinations.+-.SD of a single experiment representative of two experiments.

DETD Cell surface syndecan-1 was induced by synthetic **PR-39** in a concentration dependent manner, thereby demonstrating that syndecan-1 induction is due to **PR-39** and not to undetected trace contaminants present in the preparation from wound fluid.

DETD The results presented here demonstrate that an antibacterial peptide, **PR-39**, is in the fluid recovered from skin wounds and that it enhances the expression of cell surface syndecan-1 on mesenchymal. . .

DETD Uptake and binding characteristics of **PR-39**, Effect on Cell Permeability and Morphology

DETD The uptake and binding of **PR-39** was demonstrated as follows. **PR-39** was iodinated using the Iodogen procedure (Pierce T). The influx and efflux kinetics were calculated, accessable compartments were evaluated, and. . .

DETD Cell permeability after **PR-39** treatment was then measured. NIH-3T3 cells were cultured to confluence on chamber slides. 0, 0.1, 0.5, 1, and 10 .mu.M **PR-39** was added to the culture medium and incubated 60 minutes at 37.degree. C.; then 50 .mu.g/ml propium iodide (FW 688) was added. A 2/20.times. field of fluorescent cells shown with **PR-39**, 100% (approximately 50/20.times.) with 0.1% Triton.TM. showed no large perability changes in the membrane.

DETD . . . determine the effect on cell morphology, NIH-3T3 cells were cultured to confluence on coverslips in 24 well plates. 2 .mu.M

PR-39 was adde[redacted] the medium and cultured for 72[redacted]. 2% PFA and ace[redacted]e were used to fix cells and [redacted]s. . .

CLM What is claimed is:

3. The method of claim 1 wherein the synducin is PR-39 .

(FILE 'HOME' ENTERED AT 18:58:15 ON 23 MAR 2000)

FILE 'REGISTRY' ENTERED AT 19:00:02 ON 23 MAR 2000

L1 0 S ARG ARG ARG PRO ARG PRO PRO TYR
L2 108 S PR (3A) "39"
L3 0 S PROTOSOMASE (3A) MEDIATED (3A)DEGREDA?
L4 7 S ANGIOGENESIS
L5 0 S L2 AND L4
L6 0 S PROTOSOMASE
L7 0 S L2 AND L4

FILE 'MEDLINE, BIOSIS, CAPLUS, USPATFULL' ENTERED AT 19:10:54 ON 23 MAR 2000

L8 4 S ARG ARG ARG PRO ARG PRO PRO TYR
L9 25992 S ANGIOGENESIS
L10 2 S L8 AND L9